Sustained weight loss and acceptable tolerability with the GLP-1 analogue Liraglutided in obese non-diabetic adults

a 2-year randomized trial

Lean, Michael E. J.; Astrup, Arne; Al Hakim, Mazin; Carraro, Raffaele; Finer, Nick; Kunesova, Marie; Lindegaard, Marie L.; Niskanen, Leo; Rasmussen, Mads Frederik; Rissanen, Aila; Rössner, Stephen; Savolainen, Markku J.; Van Gaal, Luc

Published in:
Obesity

Publication date:
2010

Document version
Publisher's PDF, also known as Version of record

VOLUME 18 | SUPPLEMENT 2 | NOVEMBER 2010
www.obesityjournal.org

obesity

a research journal

Abstracts x 4

ABSTRACT SUPPLEMENT

OBESITY 2010

28th Annual Scientific Meeting

San Diego, California | October 8–12

Supplement to Obesity

OBESITY SOCIETY

nature publishing group npg

well tolerated with no significant changes in any of the safety assessments employed and showed an attractive pharmacokinetic profile suitable for a once-daily dosing regimen. In conclusion, TM38837 is a novel second generation CB1 antagonist with metabolic efficacy and potency in animals comparable to rimonabant but which in contrast to first generation CB1 antagonists has markedly reduced propensity to penetrate the blood-brain barrier. This together with an attractive safety and pharmacokinetic profile in humans makes TM38837 a promising therapy for obesity, diabetes and related metabolic disorders.

484-P
Sustained Weight Loss and Acceptable Tolerability With the GLP-1 Analogue Liraglutide in Obese Non-Diabetic Adults: A 2-Year Randomized Trial

Michael E.J. Lean *Glasgow, United Kingdom*; Arne Astrup *Copenhagen, Denmark*; Mazin Al Hakim *Almere, Netherlands*; Raffaele Carraro *Madrid, Spain*; Nick Finer *London, United Kingdom*; Marie Kunesova *Praha 1, Czech Republic*; Marie L. Lindegaard *Soeborg, Denmark*; Leo Niskanen *Kuopio, Finland*; Mads Frederik Rasmussen *Princeton, NJ*; Aila Rissanen *Helsinki, Finland*; Stephan Rössner *Huddinge, Sweden*; Markku J. Savolainen *Oulu, Finland*; Luc Van Gaal *Antwerp, Belgium*

Background: A placebo-controlled 20-week double-blind trial with open-label orlistat comparator and 84-week open-label extension investigated weight loss with liraglutide 1.2–3.0mg. 2-year results for safety/tolerability (primary outcome) and weight loss/maintenance during treatment with liraglutide 2.4/3.0mg or orlistat are presented. Design: Obese adults (18–65 years. BMI 30–40kg/m^2) began a 500 kcal/day deficit diet plus exercise, and after 2 weeks, 564 individuals were equally randomized to once-daily subcutaneous liraglutide (1.2–3.0mg) or placebo, or orlistat (120mg 3×daily). After 52 weeks, liraglutide/placebo-treated subjects switched to 2.4mg liraglutide (based on 20-week results), subsequently 3.0mg (based on 52-week results). www.clinicaltrials.gov ID:NCT00480909. Funding:Novo Nordisk, Denmark. Results: Of 398 extension participants (n=59–72/arm, age 46.8±10.1 years, BMI 34.8±2.7kg/m^2 [mean±SD]), 268 completed. *Weight loss* from randomization–2 years was 3.0kg (95% CI 1.3–4.7) greater with liraglutide 2.4/3.0mg (n=184) than orlistat (n=95) (p<0.001; intention-to-treat, last-observation-carried-forward). Completers from screening (week -3) on liraglutide 2.4/3.0mg (n=92) lost 7.8kg and those on orlistat (n=45) lost 5.4kg, a mean difference of 2.5kg (0.4–5.2) (p=0.09). More completers on liraglutide 2.4/3.0mg (75%) than on orlistat (53%) lost >5% screening weight. *Systolic blood pressure* was reduced for completers by 15.3±12.6mmHg (liraglutide 2.4/3.0mg) and 10.2±10.8mmHg (orlistat) from a mean 132±13.7mmHg at screening. The commonest liraglutide-related side-effect was nausea, mainly in weeks 1–6. Serious side-effects (mostly gastrointestinal) were experienced by 17/186 (9%) individuals on liraglutide 2.4/3.0mg and 6/95 (6%) on orlistat; 12% and 3% participants withdrew, respectively, due to (mostly gastrointestinal) side-effects. Conclusion: Liraglutide 2.4/3.0mg had satisfactory safety and tolerability, maintained higher weight loss than orlistat for 2 years, and a substantial reduction in blood pressure.

485-P
The Long-Term Effect of Tesofensine on Appetite Sensations

Jo-Anne Gilbert *Quebec, Canada*; Anne Raben, Dieter Meier *Ballerup, Denmark*; Arne Astrup, Anders M. Sjodin *Copenhagen, Denmark*

Introduction: Tesofensine (TE) is a new drug producing twice the weight loss seen with currently marketed drugs. It inhibits the pre-synaptic reuptake of noradrenaline, dopamine and serotonin, and decreases the motivation to eat. The dual aim of the present analysis was to examine the effect on appetite after weight loss following the cessation of the drug, as well as to verify the effect on appetite during an extended treatment of 24 weeks. Methods: A 24-week randomised, double-blinded, placebo-controlled trial (RCT) was followed by a drug free-period (12±3 weeks) and an open-labelled uncontrolled study (24 weeks). During the RCT subjects were divided into four treatment groups (placebo and 0.25, 0.50 and 1.00 mg of TE), and in the extension study they all received 0.50 or 1.00 mg TE. Only subjects who completed both studies were included in the present analysis. A composite satiety score (CSS) was calculated from the appetite sensation ratings [CSS=satiety+fullness+(100-hunger)+(100-prospective food consumption)] Results: TE induced a dose-dependant increase in CSS that diminished over time as weight loss continued in the RCT. Unexpectedly, after drug withdrawal CSS did not decrease beyond baseline, despite the participants' reduced weight state. The re-introduction of TE resulted again in increased CSS regardless of initial treatment/weight loss. Conclusion: We postulate that in the early phases the drug-induced increase in satiety may be the main driver of weight loss, while in the weight reduced state TE mainly contributes to weight maintenance by counteracting the increased motivation to eat often seen after weight loss.

486-P
Clinically Meaningful Weight-Loss Outcomes With Low-Dose Controlled-Release Phentermine/Topiramate in Overweight/Obese Subjects

Kishore M. Gadde *Durham, NC*; Craig Peterson, Wesley W. Day *Mountain View, CA*

Currently available weight-loss agents generally lead to only modest weight loss. A low-dose, controlled-release formulation of phentermine/topiramate (PHEN/TPM CR) was evaluated for weight loss in two randomized, placebo-controlled, 56-week Phase 3 trials. EQUIP evaluated PHEN 3.75 mg/TPM CR 23 mg (3.75/23) and PHEN 15 mg/TPM CR 92 mg (15/92) vs placebo in 1267 adult subjects with BMI ≥35 kg/m^2. CONQUER evaluated PHEN 7.5 mg/TPM CR 46 mg (7.5/46) and 15/92 vs placebo in 2487 adult subjects with BMI ≥27 kg/m^2 and ≤45 kg/m^2 and ≥2 weight-related comorbidities. In a pooled data analysis, least-squares (LS) mean percent weight loss in the ITT population (N=3678) was significantly greater for all doses of PHEN/TPM CR vs placebo: 1.5% for placebo (n=1477), 4.7% for 3.7/23 (n=234), 8.2% for 7.5/46 (n=488), and 10.4% for 15/92 (n=1479) (P<0.0001 vs placebo for all doses). In subjects completing 56 weeks of treatment on study drug (n=2193), LS mean percent weight loss was also significantly greater in all PHEN/TPM CR groups (P<0.0001 vs placebo): 2.1% for placebo, 6.0% for 3.75/23, 10.4% for 7.5/46, and 13.4% for 15/92. Significantly more PHEN/TPM CR subjects (ITT-LOCF) lost ≥10% of their baseline weight than placebo subjects: 7.4%, 18.8%, 37.3%, and 47.5% for placebo, 3.75/23, 7.5/46, and 15/92, respectively (P<0.0001 for all doses vs placebo). Greater improvements in weight-related comorbidities were documented in subjects losing ≥10% of their baseline weight. PHEN/TPM CR was well tolerated. PHEN/TPM CR is associated with significant and clinically meaningful weight loss in overweight/obese subjects.

487-P
Aliskiren/Amlodipine Combination Lowers Blood Pressure More Effectively Than Amlodipine Monotherapy in Obese and Non-Obese Patients With Moderate to Severe Hypertension

Rudiger C. Braun-Dullaeus *Magdeburg, Germany*; Sergey B. Shustov *St. Petersburg, Russia*; Carmen Alvarez *Barcelona, Spain*; Gregorio G. Rogelio *Quezon City, Philippines*; Cheraz Cherif Papst *Basel, Switzerland*; Jack Zhang *East Hanover, NJ*

Objective: To assess the antihypertensive efficacy of aliskiren/amlodipine (ALI/AML) combination compared with AML monotherapy in obese (BMI ≥30 kg/m^2) and non-obese (BMI <30 kg/m^2) patients with moderate to severe hypertension. Methods: This was an 8-week, multicenter, randomized, double-blind study. After a 1-to 4-week washout period, patients with mean sitting systolic blood pressure (msSBP) ≥160 to <200 mmHg were randomized to receive ALI/AML 150/5 mg or AML 5 mg for 1 week followed by forced titration to ALI/AML 300/10 mg or AML 10 mg for 7 weeks. At week 8, change from baseline in mean sitting BP and the proportion of patients achieving BP control (<140/90 mmHg) were assessed *post hoc* in obese (n=179) and non-obese (n=303) subgroups. Results: Patient demographics and baseline BP (obese: 169.8/95.5 mmHg; non-obese: 172.3/94.7 mmHg) were similar in the two subgroups. At study endpoint, ALI/AML significantly lowered BP compared with AMLalone in obese (-35.9/-15.1 *vs.* -30.0/-10.9 mmHg) and non-obese (-38.8/-16.8 *vs.* -31.1/-13.3 mmHg) patients (all p <0.01). ALI/AML provided significantly (p <0.05) greater BP control rate than AML in obese (61.9% *vs.* 46.1%) and non-obese (69.4% *vs.* 51.4%) patients. Both treatments were generally well tolerated in each subgroup. Conclusion: Treatment with ALI/AML combination therapy resulted in significantly greater BP reductions and BP control rates compared with AML monotherapy in both obese and non-obese patients with moderate to severe hypertension.

For author conflict of interest information, see page S228